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Strongly Fluorescent Push-Pull Substituted Carbostyrils Absorbing in the Visible

Georg Uray * Gernot A. Strohmeier and Walter M. F. Fabian

Institute of Chemistry, Karl-Franzens-University of Graz

Heinrichstrasse 28, A-8010 Graz (Austria)

georg.uray@kfunigraz.ac.at



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Contents:

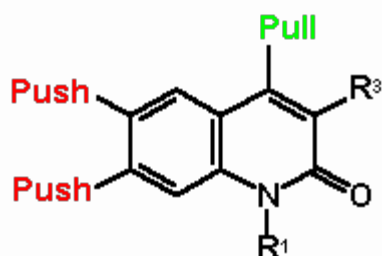
1. [Introduction](#)
2. [Structure of the investigated compounds](#)
3. [Synthesis](#)
4. [Spectroscopic Investigation](#)
5. [Calculation](#)
6. [Conclusion](#)
7. [Experimental](#)
8. [Acknowledgement](#)
9. [References](#)

1. Introduction

Previous work on differently substituted carbostyrils [1-3] has shown that only some especially substituted molecules of this substance class show interesting fluorescence properties. However, in contrast to the widely used oxa analogue coumarins strong fluorophors are scarce. Therefore principle strategies have been investigated, which substituent properties are important. What makes a carbostyril to be a good fluorophor [3]

- Donor substituents in positions 6 and 7
- a trifluoromethyl group in position 4

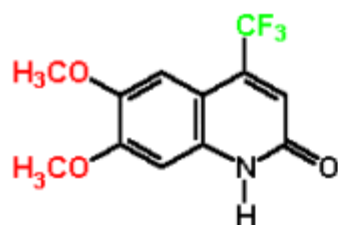
Experimental and theoretical data have shown that the position 7 influences properties like absorption and quantum yield, whereas position 6 is connected to absorption wavelength. A strong acceptor substituent in position 4 gives a significant bathochromic shift and increases the quantum yield in most of the investigated molecules.



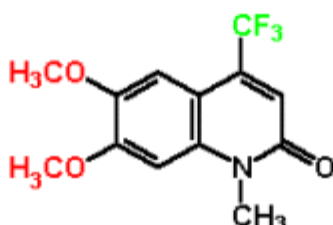
Especially acylation effects on amino functions are very interesting. The only commercially available 4-methyl-7-amino-2(1H)quinolinone (cpd **10** in this paper), sold as "carbostyryl 124" or "CS 124", 4-methyl-7-dimethylamino-2(1H)quinolinone "CS 165" and the esterase substrate 7-hydroxy-4-trifluoromethyl-2(1H)quinolinone "CS151" have very high quantum efficiency (the latter two not in this paper). However, as can be seen in the table, N7-acylation of CS 124 shifts the absorption- and emission-maxima significantly to the blue and quantum yield drops drastically. (cpd **12** in this paper).

Therefore in this work the influence of amino, alkylamino and acetylamino groups in positions 6 or 7 in combination with a methoxy group in position 7 or 6 on absorption and emission properties is investigated. In the context to CS 124, our standard 6,7-dimethoxy-4-trifluoromethyl-2(1H)quinoline **1**, which has been published recently [4], will be named CS370. 6-acetylaminocarbostryls **14** and trifluoromethylanalogue **15** were not synthesized, however, they were calculated for comparison.

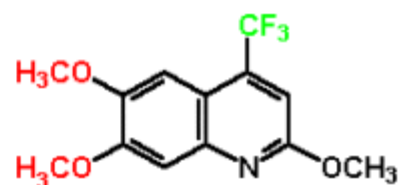
2. Structure of the investigated compounds



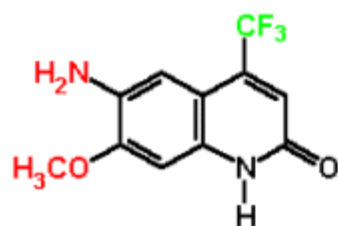
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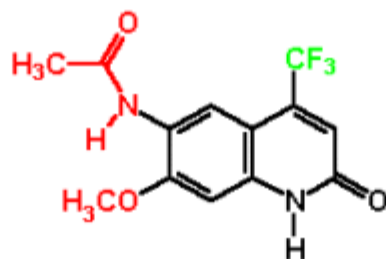
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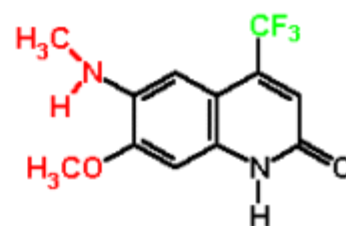
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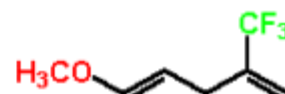
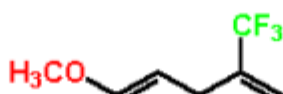
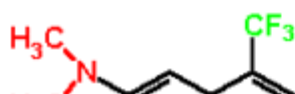
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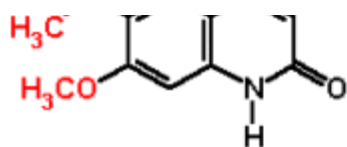


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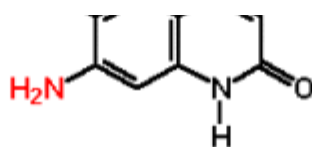


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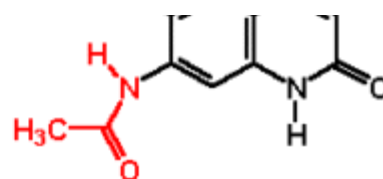




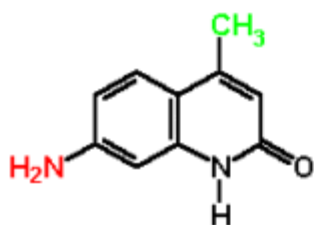
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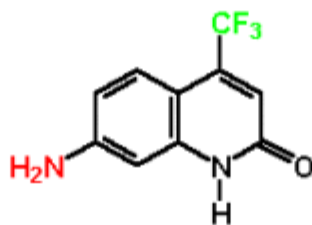
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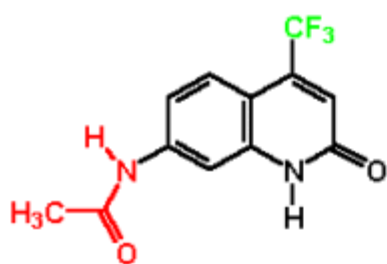
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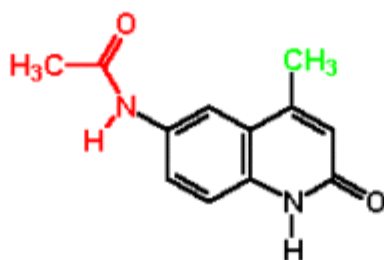
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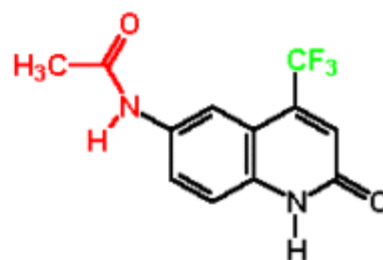
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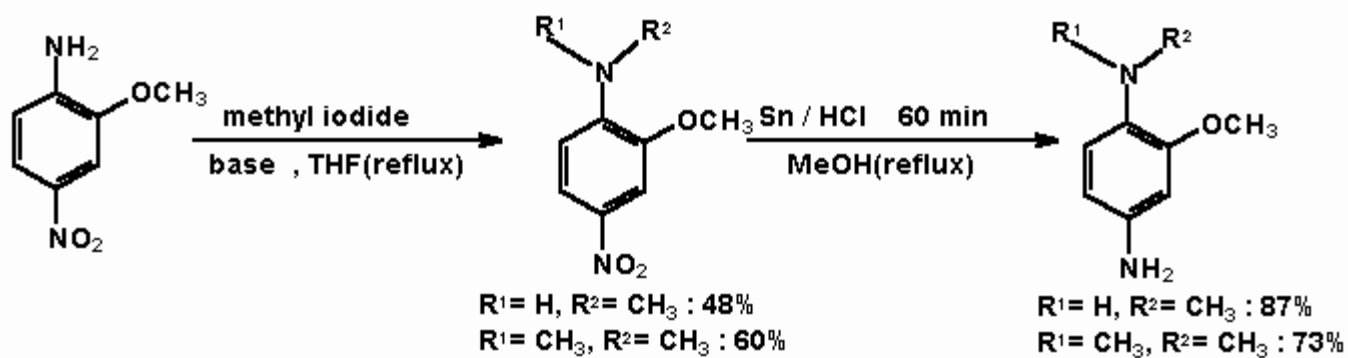


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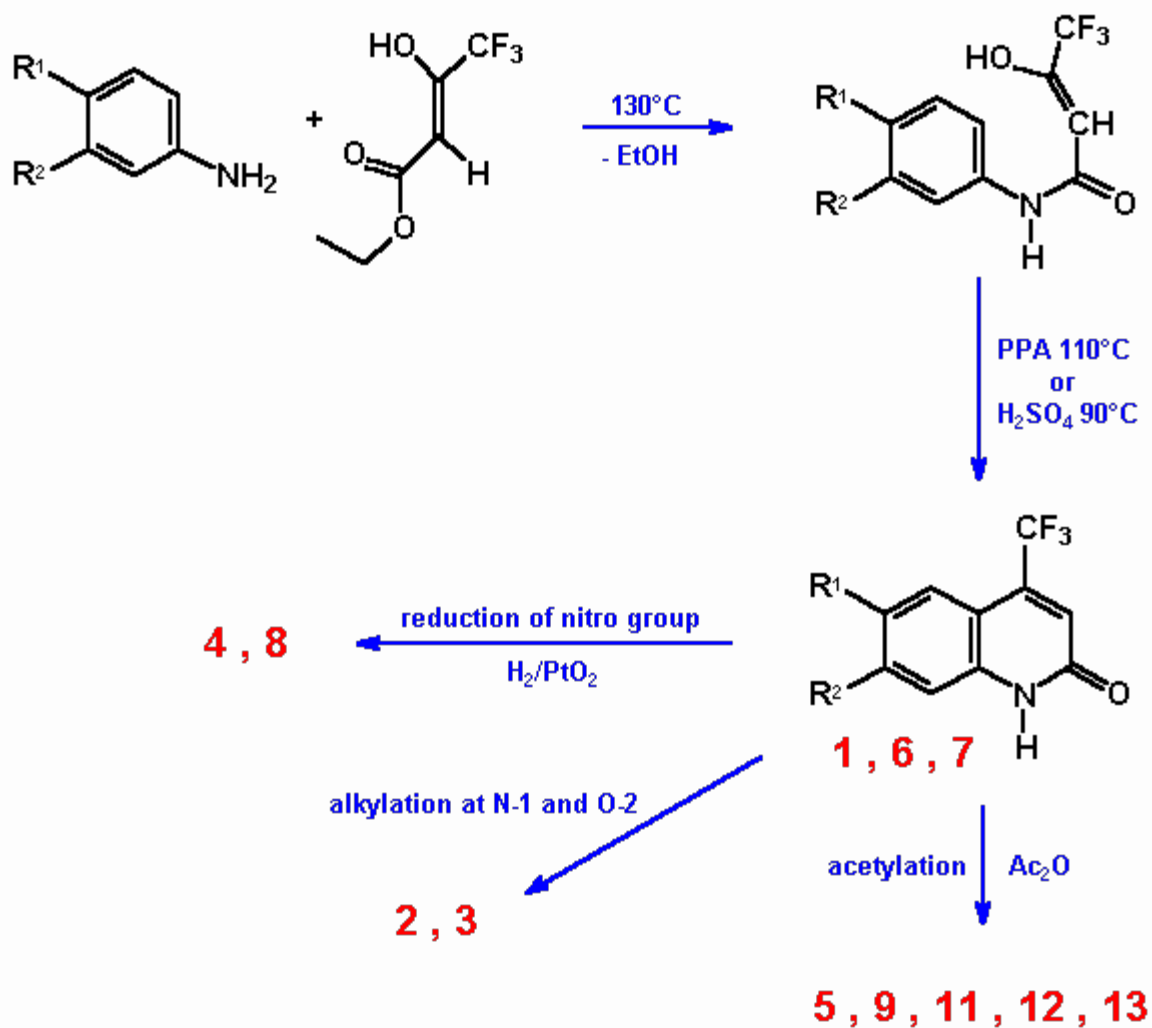


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3. Synthesis

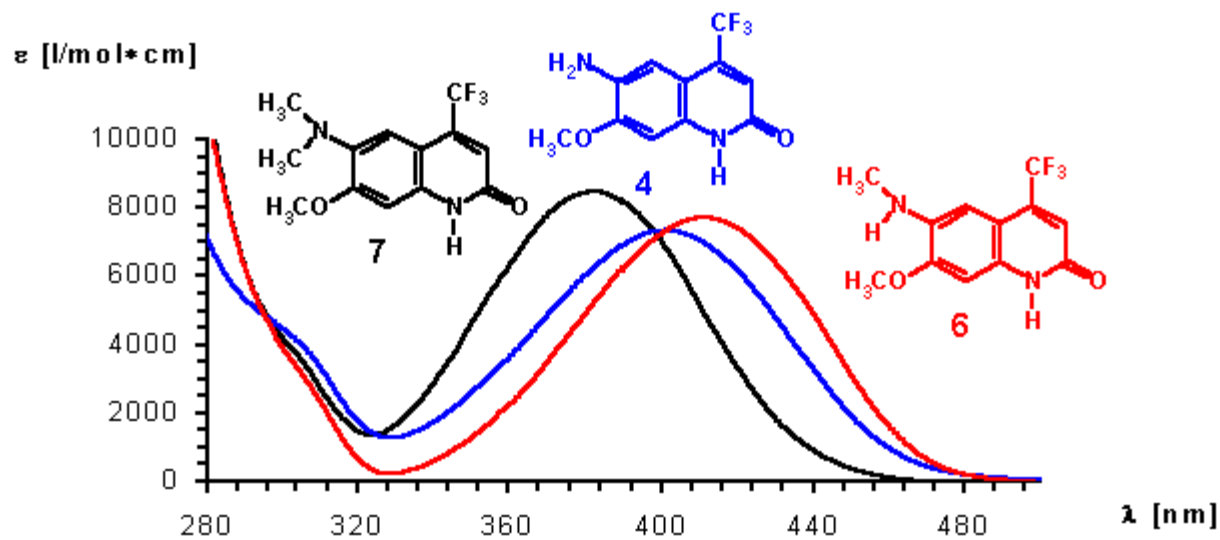


The following anilines have already been described in literature: 2-methoxy-*N*-methyl-4-nitro-aniline [5], 2-methoxy-*N,N*-dimethyl-4-nitro-aniline [6] and 2-methoxy-1-*N*-methyl-4-phenylenediamine [7].



4. Spectroscopic Investigation

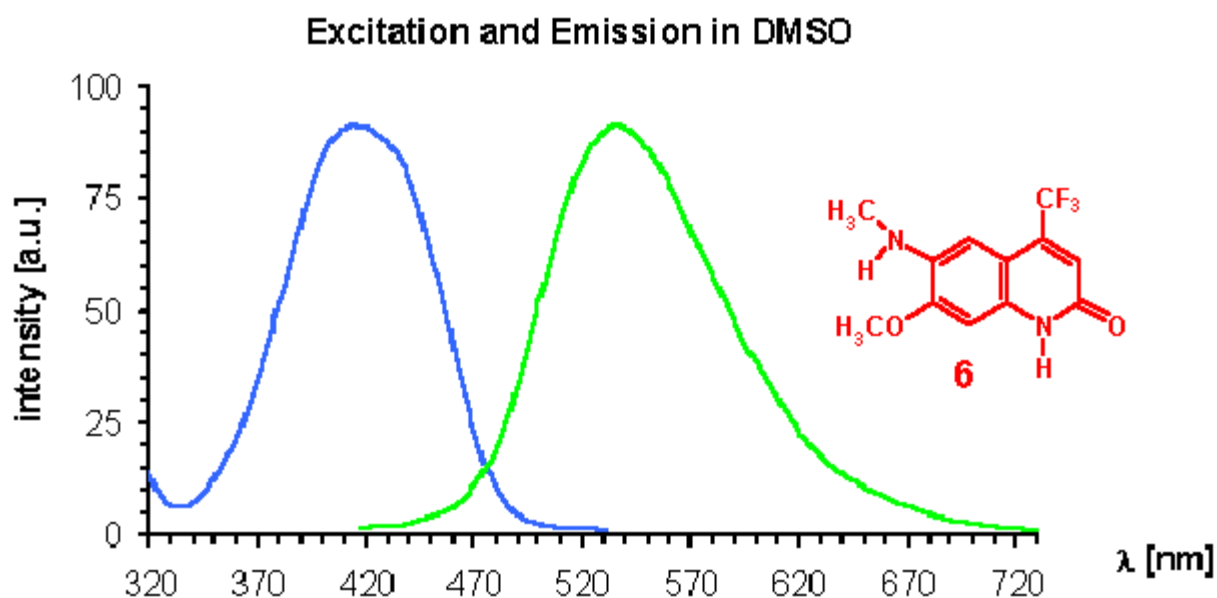
VIS-spectra in DMSO



As known for our model 2(1H)-quinolinone **CS370 1**, the newly described N-methyl derivative **2** also shows no significant difference in absorption and emission maxima to the parent compound. The observed solvent dependence is consistent with previous observations leading to significant blue shifts (about 10-15 nm in water compared with DMSO). However, O-Methylation and hence formation of a quinoline structure **3** leads to significant shorter wavelength absorption and especially small Stoke's shifts. This is a very good indicator for a quick analysis if O or N-alkylation has occurred.

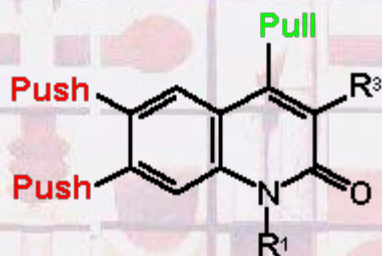
A comparison of the UV-spectra of **6-amino 4** vs methylamino **6** and dimethylaminoderivative **7** shows surprisingly the **dimethyl derivative 7** having the lowest longwave absorption maximum. As expected, **N-acetylamino derivative 6** is most blue shifted. This is also reflected in the calculation of the lowest energy structure showing the sterically more demanding dimethylamino group out of plane. However, it is very interesting also from a theoretical point of view, that the Stoke shifts of 173 nm or 214 nm as well as the emission maxima of 557 or 580 nm (in DMSO or water) are the highest values ever observed on a carbostyryl. Excitation and emission spectra of this interesting compound are displayed below.

Surprisingly, our compounds believed to be of structure **8** and **9** show **too low wavelength absorption maxima** as evidenced by comparison with analogues **7** and **8** (see yellowish fields in table). The **calculated** values support strongly, that we should think about revision of these structures, because they could be unexpected isomers. We are continuing to get a confirmation about this subject.



5. Calculations

The geometries of all investigated compounds were completely optimized by the semiempirical AM1 Hamiltonian [9] using the eigenvector following routine [10] (keyword PRECISE) as implemented in the Vamp program package [11]. Electronic excitation energies were obtained by the ZINDO program [12,13]. Bulk solvent effects (DMSO, H₂O) were included by the self-consistent reaction field (SCRF) approximation [14,15].



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[view calculated 3D-structures: click number in table!](#)

compound	solvent	ϵ	$l_{\text{abs}}(\text{exp})$	$l_{\text{abs}}(\text{calc})$	f	$l_{\text{flu}}(\text{exp})$	Stokes' shift	f
1	DMSO	10670	368	368	0.351	444	76	0.452
	H ₂ O	11560	358	366	0.352	432	74	0.241
2	DMSO	6680	370	369	0.338	438	68	0.344
	H ₂ O	6680	360	366	0.339	430	70	0.135
3	DMSO	9290	348	344	0.148	383	35	0.247
	H ₂ O	8070	345	344	0.148	383	38	
4	DMSO	7350	403	372	0.134	533	130	0.160
	H ₂ O	8720	379	369	0.315	531	152	0.071
5	DMSO	7330	368	353	0.284	448	80	0.278
	H ₂ O	6590	353	352	0.285	440	87	0.161
6	DMSO	7955	414	376	0.312	532	118	0.274
	H ₂ O	7040	389	372	0.313	544	155	0.087
7	DMSO	8470	384	351	0.335	557	173	0.120
	H ₂ O	9000	366	350	0.356	580	214	0.070
8	DMSO	6200	361	362	0.372	406	45	0.208
	H ₂ O			360	0.373			
9	DMSO	6100	342	372	0.342	376	34	0.124
	H ₂ O	6000	340	369	0.343	382	42	0.165
10	DMSO	16670	354	337	0.505	388	34	0.485

	H ₂ O	15800	341	333	0.509	416	75	0.959
11	DMSO		374	344	0.470	448	74	
	H ₂ O			341	0.473			
12	DMSO	10400	336	322	0.210	371	35	0.037
	H ₂ O	9540	327	322	0.210	366	39	0.096
13	DMSO		346	340	0.426	400	54	
	H ₂ O			338	0.430			
14	DMSO			348	0.146			
	H ₂ O			346	0.146			
15	DMSO			348	0.177			
	H ₂ O			347	0.177			

6. Conclusion

As shown in our recent publication, push-pull substituted carbostyrils in position 6,7 and 4, respectively, have absorption maxima close to the visible region.

The large bathochromic shifts are coupled mainly due to the influence of electron donating groups in position 6 of the ring system. Monoalkylated 6-amino groups in combination with a 7-methoxy group give the largest red shifts (UV maximum: 414 nm for compound 6 in DMSO), whereas dialkylated 6-amino groups give the largest Stokes shifts (173 nm in DMSO respectively 214 nm in water for compound 7). It is interesting to note that acetylated 6-amino groups have about the same impact on photophysical properties as methoxy groups (compare 1 with 5).

Quantum yields are typically at least 0.1. As expected, non acylated amino substituents in position 7 exhibit the strongest electron donating effects increasing quantum yields significantly. In most of the investigated cases intensities are lower in water as solvent compared with polar-aprotic DMSO.

From our previous experience [3,4] one can expect quite good agreement between calculated and experimental absorption maxima. There is, however, one notable exception: the donor properties of amino groups, and hence the bathochromic shift induced thereby, is greatly underestimated by the ZINDO procedure (see e.g., results for **4**, **6**, **10**, **11**). This seems to be a quite general shortcoming of this semiempirical quantum chemical method. For the other derivatives the agreement between experiment and calculation is quite satisfying. From the present results one can conclude that an acylamino group is comparable in its effect on absorption maxima to an alkoxy function.

According to this set of data we can suggest that 6,7-diamino substituted carbostyrils, especially the ones with monoalkylated amino groups should provide more excellent photophysical properties compared with the compounds presented in this paper. This new fluorophors can serve as potent competitors to the widely used coumarins especially because of the advantage of a better photochemical and thermal stability.

In short we have prepared highly fluorescent carbostyrils with absorption maxima up to 414 nm and it is evident that this range can still be extended preparing 6,7-bis-N-alkyl derivatives.

7. Experimental

Synthesis of Carbostyrils: General Procedure Carbostyrils were prepared by Knorr reaction, which afforded anilines and β -keto esters. Substituted anilines were added to hot ethyl (or isopropyl) 4,4,4-trifluoroacetoacetate and heated until the removal of alcohol had stopped. Then cyclisation was performed in concentrated sulfuric acid or polyphosphoric acid. The overall yield was about 30 to 60 % in most of the cases. Carbostyrils that resulted from nitro-anilines were reduced under heterogeneous catalysis (PtO_2/H_2) to give the desired amino derivative.

Measurement of UV- and Fluorescence Spectra The measurement of the uv spectra was performed at concentrations of 4×10^{-5} mol/l. From that data calculation of the absorption coefficient was done according to Lambert-Beer's law: Fluorescence spectra were recorded at concentrations of 4×10^{-6} mol/l. The quantum yield was calculated from the area (integration) of the uncorrected emission spectra by comparison with standard substances (quinine sulfate [8], 4-methyl-carbostyryl [3]). Calculation was done by Parker's equation.

Instrumentation The UV/VIS spectra were recorded on a Shimadzu uv/vis scanning spectrophotometer UV-2101PC at room temperature. Excitation and emission spectra were obtained using a Shimadzu RF-5001 PC spectrofluorophotometer. The spectrofluorophotometer is fitted with a 150W xenon lamp operated as a continuous wave source, slits selectable in 6 steps to produce spectral bandwidths of 1.5, 3, 5, 10, 15 and 20 nm, and an R452-01 photo multiplier. Excitation and emission monochromators: ion-blazed holographic concave grating F/2.5.

8. Acknowledgement

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9. References

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